Does Pulmonary Surfactant Aid in Defense of the Lungs?

The involvement of the pulmonary surfactant system in defense of the alveoli and distal airways of the lungs is an aspect of respiratory physiology and toxicology that has been largely overlooked. The pulmonary surfactant system is absolutely critical to survival of all mammalian species, as progressive loss of surfactant leads to lung collapse and death of the organism. In recent years it has been noticed that under certain circumstances, especially those involving the inhalation of dust, the lungs may respond by increasing the production of surfactant. The purpose of this reaction is unclear although it seems reasonable that the overproduction of surfactant represents a little-known defensive posture of the lungs.

Pulmonary surfactant is a complex mixture of surface active phospholipids and specific proteins that stabilize the alveoli and distal airways of the lungs. The phospholipid component consists of approximately 60% saturated and 40% unsaturated phospholipids. The saturated phospholipids are primarily responsible for lowering surface tension at the air–cell interface, but the function of the unsaturated components is not known. All components of surfactant are synthesized and secreted by alveolar type II cells.

Pulmonary surfactant exists in two major compartments in the lungs, the intracellular or storage compartment in the cytoplasm of alveolar type II cells and the extracellular compartment in the alveoli and distal airways. Under normal circumstances these two pools of surfactant exist in dynamic equilibrium such that the size relationship between the two pools is maintained relatively constant. Many toxicants, both chemical and particulate, appear to interfere with this relationship (*1*).

Exposure to silica is an especially effective stimulus that causes massive increases in both intra- and extracellular surfactant compartments. The condition induced in the lungs of rats by inhaled and/or intratracheally instilled silica closely resembles the human lung disease known as pulmonary alveolar proteinosis. The etiology of pulmonary alveolar proteinosis is not known; however, in this disease surfactant proteins and phospholipids accumulate in the alveoli and distal airways and interfere with gas exchange in the same way as in acute silicosis. The similarity between alveolar proteinosis and acute silicosis was first noted by Heppleston and coworkers more than 20 years ago (*2*), but in the intervening period little progress has been made toward understanding the relationship between these two debilitating lung diseases.

Lung diseases resulting from the inhalation of silica and silicates occur in a wide variety of industries. In developing countries, where less attention is given to rigid health standards, the prevalence of dust-induced lung diseases continues to increase. Even in the industrialized nations, where protection of workers is a high priority, subclinical evidence of lung disease is common. Inhalation of silica dust can give rise to two distinct disease states known as acute silicosis and chronic silicosis. Acute silicosis generally occurs in the lungs of humans within a relatively short period of time after exposure to silica, a period ranging from a few months to a few years. Chronic silicosis develops over a period of many years and may take as long as 20 years before it is debilitating. The relationship between acute and chronic silicosis is not clear, although one might lay the foundation for progression into the other.

Pulmonary surfactant accumulation can be induced in the lungs by numerous other toxic agents, either particulate or chemical. Particulates other than silica known to induce surfactant accumulations in the lungs include asbestos, aluminum, bismuth orthovanadate, cement, chromium dioxide, fiber glass titanium dioxide, nickel, and diesel exhaust. A wide variety of chemical agents also induce a surfactant response including busulphan, bleomycin, cadmium, ambroxol, and cationic, amphiphilic drugs such as amiodarone, chlorphentermine, and propranalol. The question is, what do these different agents have in common and what protective role, if any, does the stimulation of surfactant production play in the lungs? Insofar as common factors are concerned, the initial focus must be directed to the source of surfactant, the type II cells. It has been shown that in the case of silica, many alveolar type II cells are in an activated metabolic state: "activated" in the sense that they can synthesize surfactant at a rate many times greater than normal type II cells. The activated type II cell is recognized by its hypertrophic appearance coupled with the presence of large numbers of cytoplasmic surfactant storage organelles known as lamellar bodies. Hypertrophic type II cells have also been reported in the lungs of animals exposed to other toxic chemicals and particulate agents, and presumably these "super" type II cells are also engaged in the hypersecretion of surfactant.

Another common feature is an inflammatory reaction in the lungs of exposed animals, generally manifested by the presence of neutrophils in the alveoli. It is possible that a factor secreted by one of the many kinds of inflammatory cell seen in the lungs and alveolar spaces might stimulate surfactant production by alveolar type II cells. Perhaps such a factor might arise from macrophages or neutrophils.

Finally, what is the purpose of surfactant hypersecretion? Could excessive phospholipids in the alveoli and distal airways protect the lungs against the cytotoxic effects of these numerous agents? It has been shown that lungs can be protected against the lethal effects of nitrogen dioxide by increased alveolar phospholipids induced by chlorphentermine. Surfactant phospholipids also appear to reduce the cytotoxic effects of silica. One possible mechanism that might account for these protective effects of surfactant involves the quenching of free radicals by the unsaturated phospholipids of pulmonary surfactant. Unquenched free radicals would lead to lipid peroxidation and tissue damage. This general mechanism could be invoked when any free-radical-generating agent entered the lungs. Activation of type II cells and their hypersecretion of surfactant phospholipids would then be a protective response of the lungs against the damaging effects of free radicals.

Gary E. R. Hook
Co-editor-in-Chief

References

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2. Heppleston AG, Young AE. Alveolar lipoproteinosis: an ultrastructural comparison of the experimental and human forms. J Pathol 107:107–117(1972).